

Women and Adverse Drug Reactions Reporting in the Canadian Context

a discussion paper
prepared by Colleen Fuller for

Women and Health Protection



October 2002
Final Draft
Revised: August 2003

Introduction

Women's health issues have been defined as “any matter that affects the health of women exclusively, that impacts predominantly on women's health (at any age), or that affects women's health differently from that of men”¹. An effective strategy to support women’s health addresses all of these matters, including the approval, use and regulation of prescription drugs.

The purpose of this paper is to provide an overview of how Canada’s program for reporting Adverse Drug Reactions (ADRs) supports – or doesn’t support – an effective women’s health strategy related to prescription drug use. Women are at greater risk of exposure to unsafe medications and drug interactions², something that was recognised in 1996 when new guidelines were introduced in Canada requiring the inclusion of women in clinical trials³. The guidelines flowed from Health Canada’s commitment to develop and apply a Gender-Based Analysis (GBA) to programs, policies and legislation. However, thus far, a GBA has not been applied to Health Canada’s program of post market surveillance.

The paper offers an overview of the current ADR reporting system, including the steps taken to improve both the reporting system itself and the flow of ADR information to health providers, patients and the public at large. It includes a review of the literature about the public policy environment governing women and prescription medicines, specifically the environment in which reports of adverse drug reactions are received, analysed and utilised to develop and/or improve the national Women’s Health Strategy. The paper summarises the various factors that may influence the increased frequency of adverse events associated with women’s prescription drug use, including direct-to-consumer-advertising (DTCA), fast-tracked drug approvals, deregulation, extended patent protection and trade liberalisation.

This paper does not explore in detail the larger issue of drug safety and drug effectiveness though it touches on related materials and may be a topic for the future for Women and Health Protection.

Thalidomide, DES and the Dalkon Shield: The Questionable Legacy of Women and Drug Safety

The development of Canada’s prescription drug policies and regulations has been shaped by forces which often appear to be pulling in opposite directions – the industry, on the one hand, and the consumer’s health movement, on the other, with government showing favour to both camps, depending on the political climate of the day. Women in both the developed and developing world often were found in the leadership of the consumer’s health movement and in campaigns for tougher rules governing the drug industry and the market for prescription medicines. As early as 1908, for example, the temperance movement organised successfully for

¹ Proceedings, National Conference on Women's Health, Public Health Reports (Suppl) 1987; 102: 1-3; July, 1987 / August, 1987, US Department of Health and Human Services

² Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *British Journal of Clinical Pharmacology* 1998; 46(5):505-511

³ These guidelines are considered by some to be relatively weak (for example, in comparison with comparable guidelines in the United States) but nonetheless an indication of some action in response to the issue.

passage of the *Proprietary and Patent Medicines Act* in the United States – designed to weed out medicines that contained coca, opiates, strychnine and arsenic.⁴ Similarly, women were active in efforts to restrict the advertising of medicines that were sold in Canada. This led, in 1919, to amendments to the Act preventing manufacturers from making bogus, misleading or exaggerated claims for their drugs – including claims of miracle cures – and four years later, to a new law requiring drug manufacturers to list ingredients on product labels.⁵

Canada's modern system of drug regulation was developed in the early 1960s in response to the thalidomide disaster. Thalidomide was used by pregnant women in Canada for about three years, 1959 to 1962, to prevent morning sickness. Its use in North America and Europe prompted a wave of regulatory reform after the drug was found to cause peripheral neuritis and severely malformed limbs in newborns.⁶ Dr Frances Kelsey, a medical officer with the US Food & Drug Administration assigned to the thalidomide file, refused to approve the drug after reviewing the clinical evidence submitted by the manufacturer to support its application for approval in September 1960. In spite of mounting pressure from the company, Kelsey delayed the application long enough for the crisis to become known in North America. By the autumn of 1961, the company withdrew its application for approval after mounting evidence from Europe pointed to a tragedy affecting thousands of children.⁷

Although thalidomide was available in the US in sample form, it was never licensed, thanks in large part to Kelsey's strong stand at the FDA, reducing the number of newborns affected to about 17, according to the War Amps of Canada. This compares well to the estimated 135-200 Canadian children who continued to be exposed to thalidomide until it was pulled from the market in March 1962, more than three months after it had been banned in Britain and Germany.⁸ In the immediate wake of the disaster, Canada's Food and Drugs Act was amended to minimise the risk of people exposed to new drugs and to require the manufacturer to provide "full information" pertaining to "animal or clinical experience, studies, investigations and tests conducted by the manufacturer or reported to him by any person concerning that new drug".⁹

The thalidomide crisis coincided with rising interest among Canadian women in the links between health, sex and gender.¹⁰ The modern women's health movement grew out of a feminist critique during the 1960s of the medical industry as an institution of social control over women and the demands for choice on abortion in the 1970s. Women began to organise and demand changes in the way medicine was practised, arguing that physicians, in particular, ignored

⁴ Mitchell, Chester N. Deregulating Mandatory Medical Prescription, *American Journal of Law & Medicine*, 12 Am. J.L. & Med. 207 (1987)

⁵ Nonprescription Drug Manufacturers Association of Canada, *The Evolution of Canada's Self-Care Products Industry*; Accessed May 23/02: <http://www.ndmac.ca/industry/H-index.html>

⁶ See Robinson, Jeffrey, *Prescription Games: Money, Ego and Power Inside the Global Pharmaceutical Industry*, Toronto: McClelland & Stewart, 2001.

⁷ Gloria Lau, "Dr. Frances Kelsey – Her Determination Saved Thousands From Birth Defects", *Investor's Business Daily*, September 27, 2001.

⁸ Thalidomide Victims Association of Canada, "What is Thalidomide?" Accessed at <http://www.thalidomide.ca/english/wit.html> on May 24, 2002.

⁹ Volume I, Report of the Thalidomide Task Force to the Minister of National Health and Welfare, *War Amputations of Canada*, Ottawa: 1989.

¹⁰ Sex refers to biological characteristics such as anatomy and physiology. Gender refers the range of socially-determined characteristics among men and women, for example attitudes, values, relative power and influence. See *Health Canada's Gender-based Analysis Policy*, Ottawa: Public Works and Government Services Canada, 2000.

problems that were experienced mainly or exclusively by women. A case in point was DES (diethylstilbestrol), a synthetic hormone developed in 1938 and prescribed to an estimated 200,000 to 400,000 Canadian women to prevent miscarriage.¹¹ Thirty years later, DES was linked to a number of health problems in daughters exposed to the drug in the womb, including reduced fertility, complications in pregnancy and a rare form of vaginal cancer. DES Action groups were created in Canada, the U.S. and several other western countries to address the information and support needs of the DES-exposed as well as to lobby their respective governments for improved health protection laws.

This activism led to the creation of many organisations dedicated to increasing access to safe reproductive health services, protecting abortion rights and establishing abortion as a medically necessary service within the public health insurance system, and expanding community based, multi-disciplinary primary care models of health services delivery. Some of this energy was devoted to problems that had occurred when women used specific prescription drug or medical devices. For example, experiences with the Dalkon Shield led in the late 1980s to the creation of Dalkon Shield Action Canada, a Vancouver-based group representing 7,000 victims pushing for a public enquiry into why Ottawa didn't recall the contraceptive until 1985, nine years after the manufacturer had withdrawn the device and was facing litigation from 320,000 American women.¹²

These activities, along with a number of important developments outlined below, contributed to a growing interest in and focus on health protection and prescription medicines.¹³ The gender biases that had already been identified in the health sector were also undermining the ability of Canada's system of health protection to serve the needs and interests of women. By the end of the 1980s, many women had begun seriously questioning what they were sometimes being prescribed, and it was clear the health protection system was in need of major reform.

The 1990s: A Decade of Change and Reform

In July 1998, Health Canada issued a discussion paper to kick-start what it called "HPB Transition", a three-year process of "review, consultation and renewal of our health protection activities".¹⁴ HPB – the Health Protection Branch – had been created in 1972 and included the Food Directorate, Drug Directorate, Environmental Health Directorate and the Laboratory Centre for Disease Control. The rationale behind the extensive review, the paper stated, was ostensibly a perception that Canada's health system had not kept up with the latest scientific discoveries and new technologies, on the one hand, and the new risks and diseases Canadians were increasingly

¹¹ "Direct-to-consumer advertising of prescription drugs", Prepared by the Working Group on Women and Health Protection for the Direct-to-Consumer Advertising (DTCA) Consultation Workshop (undated), accessed on-line at <http://www.web.net/~desact/anglais/legisl/5direct.html> on 28 July 2002.

¹² Lynda Hurst, "Protecting our health: Is Ottawa doing its job?" Toronto Star, March 25, 1989; Dror Ben-Asher, In Need of Treatment? Merger Control, Pharmaceutical Innovation, and Consumer Welfare, J. Legal Med. 21: 3, September, 2000.

¹³ See Lefebvre, Yvonne, Women's Health Research in Canada, A Canadian Perspective. Health Canada: Ottawa June 1996 for more information about the activities of Canada's women's health movement and the organisations that resulted.

¹⁴ Health Protection for the 21st Century: Renewing the Federal Health Protection Program, July 1998, Health Canada: Ottawa, 1998.

exposed to, on the other hand. Five areas were included in the review: science, surveillance, risk management, legislation, and program development.

The women's health community welcomed the review of Canada's health protection system, but it wasn't the technological and scientific lag that they identified as the culprit behind the disasters uppermost in the public's mind. A paper prepared by the Women's Health Clinic in Winnipeg in November 1998 was sharp and to the point: Citing a growing lack of confidence in the Health Protection Branch, the group said, "The HPB is drifting into the role of protecting [the pharmaceutical] industry and its economic growth and abandoning the role of protecting the health of Canadians". The Clinic, after several months of public consultations, identified other factors that contributed to this "drift", including:

- funding cuts which "deprived the Branch of its ability to set and enforce standards independent of industry influence";
- an absence of sensitivity to issues of gender, culture, class or power and an increasing lack of ability to see or respond to the Canadian public/consumer (as opposed to industry or professionals) as either the real "client" or "partner" in meeting the HPB mandate; and
- a lack of new criteria for "safety", new methods for post marketing evaluation of drugs and devices and social and ethical evaluation of new initiatives.

These views were shared by women's health and advocacy groups across the country, and led DES Action Canada, with start-up funding from the Centres of Excellence for Women's Health Program, to form a coalition to monitor the process of legislative renewal to ensure that women's health issues were addressed. The coalition, formed in September 1998, was called the Working Group on Women and Health Protection. Still active today (its name shortened to "Women and Health Protection"), it includes women's health advocates, consumer and public interest organisations and academic researchers.

Early in 1999, then-Health Minister, Allan Rock, unveiled the Women's Health Strategy, a framework that promised to integrate a "gender-based analysis" across the department's program and policy development work. "Two important pillars of the Strategy," Rock said, "are the Canadian Women's Health Network and the five Centres of Excellence for Women's Health," both of which would continue to receive funding from Health Canada. The strategy identified four objectives, including "effective post-market surveillance and adverse events monitoring systems that safeguard women's health".¹⁵

In July 2000, Health Canada embarked on a major realignment within the ministry, creating seven branches, six regions and two agencies. Among the new branches was the Health Products and Foods Branch (HPFB) (replacing the Health Protection Branch), with a mandate to maximise "the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system". Six new regional director positions were created to maintain broad networks of contacts across the country and to work with other federal departments and provinces in the region.

¹⁵ Women's Health Strategy, Health Canada - Women's Health Bureau: Ottawa, March 1999.

Less than a year later, on April 5, 2001, Health Canada unveiled three new Directorates in the Health Products and Foods Branch to replace the Therapeutic Products Programme: the Therapeutic Products Directorate (TPD); the Biologics and Genetic Therapies Directorate (BGTD); and the Health Products and Foods Branch Inspectorate (HPFBI).

Crises sparked change

A review of developments over the decade of the 90s reveals what influences were at play in these changes. In time-honoured tradition, it was a series of disasters and crises which led to the changes begun in 1998 by the HPB Transition. But there were other government actions that contributed to a rising sense of doubt in Canada's ability to exercise control over the whole area of pharmaceutical drugs and devices. Among these was Bill C-91, a bill passed in the House of Commons in 1993 extending patents on new pharmaceutical drugs to 20 years. Critics of the legislation predicted that Canada would lose control over drug costs, and by the end of the decade it appeared that they were right.

1993 was also the year that Health Canada established the Women's Health Bureau with a mandate to enhance the responsiveness of the Canadian health system to the health needs and concerns of women. The Bureau was part of the Liberal Party's 1992 "Red Book" which promised \$13 million to support women's health research. The creation of five Centres of Excellence for Women's Health in 1995, co-ordinated by the Women's Health Bureau, was also part of this commitment.

While concerns were mounting about the impact of Bill C-91 on Canada's drug costs, other events were focusing Canadians' attention on how poorly drugs were being monitored for safety. In 1993, the federal department of health removed Meme breast implants from the market after some patients experienced immune-system problems that they associated with silicone leakage. But it was the appointment that year of Justice Horace Krever to investigate what became known as the "tainted blood scandal" that would bring the Health Protection Branch under intense public scrutiny.

The Commission of Inquiry on the Blood System in Canada (the Krever Commission) cast a long shadow over how the public viewed the country's health protection system. Although the focus of Justice Krever's report was the safety of blood products, it touched on almost every aspect of the system that was supposed to protect the health of Canadians who depended on prescription drugs and medical devices. Krever's report, submitted after a four-year investigation, criticised Health Canada for its lax monitoring, which he said was responsible for the failure to protect Canadians from blood products infected with HIV and Hepatitis C. The continuing safety of blood components and blood products, he said, depended on an active program of post-market surveillance. "One of the most important aspects of post-market surveillance," he said, "is the reporting of adverse drug reactions..." He recommended that the reporting system be expanded to include "networks of scientists and physicians to investigate adverse reactions" and to report the results of the investigations to physicians.¹⁶

¹⁶ Commission of Inquiry on the Blood System in Canada: Final Report (Krever Commission), p. 1069, Canadian Government Publishing: Ottawa, 1997.

By the end of the what had become a tumultuous decade on the drug safety front, Health Canada was facing three RCMP investigations, the first two focusing on the failure of the HPB to adequately protect Canadians from tainted blood and the finding by the Information Commissioner that Health Canada officials had destroyed potentially crucial evidence under pressure from the Red Cross – which feared victims would be able to use the documents in lawsuits.

The third RCMP investigation involved allegations that Health Canada officials had failed to withdraw the Meme breast implant until 1993 despite knowing that it wasn't safe. “. . . It's hepatitis C all over again,” predicted Dr. Pierre Blais, a former HPB scientist who had been fired for leaking an internal memo to the media that described the implants as “unfit for human implantation.”¹⁷ Despite Dr Blais' warnings, the breast implants, approved in 1969, remained on the market. By the time they were withdrawn in 1998, between 50,000 and 150,000 Canadian women had had them implanted after receiving mastectomies or for cosmetic reasons. In 1999, nine Saskatchewan women launched a class action suit against the federal government for failing to be vigilant in the regulation of breast implants in Canada. Health Canada, the women charged, was “high-handed, outrageous, reckless, wanton, entirely without care, deliberate, callous, disgraceful, wilful, in disregard of the plaintiffs' lives, safety and rights, indifferent to the consequences and motivated by economic considerations”.¹⁸

The investigation of Health Canada for its activities regarding the Meme breast implants and blood products took place two years after the resignation of Dr Michele Brill-Edwards, the senior physician responsible for drug approvals at the HPB. Dr Brill-Edwards resigned after charging that HPB officials ignored independent research suggesting the controversial heart drug, nifedipine, could actually cause heart attacks if used over a long period of time. Dr Brill-Edwards charged that the pharmaceutical industry influenced the drug approval and monitoring process at Health Canada and called for a public enquiry into how decisions were made at the department. Such an enquiry was not launched.

In addition to scandal and allegations of wrong-doing and recklessness, the Branch was also struggling to survive budget reductions of more than 50 percent between 1993/94 and 1999/2000, and the closure or downsizing of laboratories across the country. All of these problems undoubtedly influenced the First Ministers' conference held on September 11, 2000. Public expenditures for prescription drugs were caught in what seemed a relentless upward spiral. The federal government was under growing pressure from health activists, unions, seniors groups and women's organisations to act on Liberal Party commitments made in the 1997 election to set up national home care and pharmacare programs. Employers were also interested in a public pharmacare program, warning federal and provincial governments that employer-sponsored benefits were at risk, in large part because of rising prescription drug costs.¹⁹ Along with other large private payers, employers complained they were increasingly forced to determine “which drugs to cover and under what conditions”, and demanded assurances that “the

¹⁷ Laura Eggertson, “Women take on Ottawa over breast implant risk”, Toronto Star, January 2, 1999

¹⁸ Laura Eggertson, “Women take on Ottawa over breast implant risk”, Toronto Star, January 2, 1999

¹⁹ *Prescription Drug Coverage For Ontario: Planning For the Future*, A Submission of The Employer Committee on Health Care - Ontario (ECHCO) To The Honourable Elizabeth Witmer, Minister of Health, Government of Ontario, November 1997

federal government is reviewing processes and regulations to ensure that generics are not unnecessarily delayed.”²⁰ At the same time, provincial premiers were demanding that a strategy be developed to bring the rapidly escalating costs of prescription drugs under control.

The first ministers had agreed in September 2000 to develop strategies that would tackle the question of what was described as the “cost-effectiveness of prescription drugs”. Among the ideas agreed upon were:

- an intergovernmental process to assess drugs for potential inclusion in public pharmacare plans;
- an examination of current best practices and various means of addressing drug purchasing costs;
- a stronger system of post-market surveillance of prescription drugs; and
- identifying tools to ensure “the optimal use of pharmaceuticals in health care”.

By the end of the 1990s it was clear that Canada’s system of health protection was in crisis. Public confidence had plummeted in the face of a number of grave health disasters over two decades that had resulted in death and disability to many people. Not surprisingly, the “HPB Transition” unveiled by the health minister in 1998 was viewed with some scepticism and concern by the consumer and women’s health communities. They viewed the trend towards fast-tracking and the loosening of controls on testing to be dangerous signs for the public and for women in particular. They addressed concerns that the clout of the pharmaceutical industry was putting public health in jeopardy. This concern sparked a renewed and on-going activism around health protection issues, including post-market surveillance. Disconcerting developments in the health protection field have created a focus in the past few years for organisations involved in public and health policy to examine more closely the role of the pharmaceutical industry in Canada's health care system.

²⁰ A Presentation To Commissioner Romanow and The Commission on the Future of Health Care in Canada, Employers Committee on Health Care – Ontario and the Employers Committee on Health Care – Alberta

Vanessa Young

The pressure on federal and provincial governments to reassert some control over prescription drug costs and utilisation came from a diverse spectrum of interests during the latter half of the 1990s and into the new century. However, it was the death of 15-year old Vanessa Young in March 2000 that seemed to put a very human face on the failures of Canada's system of post-market surveillance. Ms Young suffered from bulimia when she began using cisapride, a drug used for a wide variety of stomach disorders. A coroner's inquest into the young woman's death held in March 2001 criticised the federal government for not acting sooner on information it had about the risks associated with cisapride when she died. This information – that patients with a number of conditions, including bulimia or anorexia, should not use the drug - was available to Canadian doctors through the medical literature but the government had failed to officially communicate that information to them, unlike in the United States. The coroner's four-person jury, which met for 16 days, could not decide who was responsible for Ms Young's death under Ontario's Coroner's Act and focused, instead, on the steps Health Canada should take to ensure it never happened again. It called for a sweeping review and a complete overhaul of the system overseeing the way prescription drugs are handled in Canada.

The jury made 59 recommendations in a report released in April 2001, 14 of them directed at Health Canada. Much of the jury's focus was on the collection and distribution of information about serious adverse drug reactions to patients and health-care providers. The jury's first recommendation called on Health Canada to set up a joint body to review, improve and standardise all communication tools and techniques, such as product monographs, warning letters, media releases and fact sheets used to inform health care professionals and consumers. Citing evidence that Canada's system of voluntary reporting of adverse drug reactions was inadequate, the jury's key recommendation called for a national system for the mandatory reporting of adverse drug reactions. Mandatory reporting, the jurors said, would "enable Health Canada to more quickly compile information and act on potentially dangerous situations". They called for a template for Drug Information for Patients to be completed and submitted by drug companies for approval and inclusion in a Product Monograph. The monographs, they said, should be clear, concise and easy to understand by the general public.

The jury urged Health Canada to produce a monthly bulletin highlighting new drug information. They were very clear about the importance of information to the public about adverse drug reactions (ADRs), recommending that a website be developed as a first priority so that ADR Report summaries could be available on the Internet. They said visitors to the website – which should use lay terms and provide links to product monographs and warnings to professionals – should be able to search for information by product/generic name. The jurors also said Health Canada should establish a 1-800 number for consumers to obtain prescription drug information. Finally, as if aware of the many recommendations which had been shelved and forgotten by the federal government in the past, they urged that appropriate resources be allocated by Health Canada so that their recommendations would be acted upon.²¹

A year later, Health Canada announced it was opening the Marketed Health Products Directorate (MHPD) within the Health Products and Food Branch. According to Diane Gorman, Deputy

²¹ Verdict of the coroners jury, Office of the Chief Coroner, 24 April 2001, Dr David Eden, Coroner.

Minister of Health, “Creation of the new MHPD is part of the re-alignment efforts by the HPFB toward a strengthened and consistent risk management approach”.²² According to Jacques Lefebvre, a spokesperson for Rx&D, the impetus for the change was the death of Vanessa Young.²³ While it was clear the MHPD was part of the on-going reorganisation initiated in 1998, Health Canada, too, was anxious to link its enhanced post-market surveillance and reporting to the Coroner’s Inquest and the 14 recommendations directed at the department. In a report issued in late August 2002, Health Canada outlined how it was meeting the targets set for it by the inquest.²⁴ It identified four on-going activities it said were designed to “enhance the drug safety system and further enhance our ability to protect the health of Canadians”. These included “the provision of timely and direct information on health risks faced by Canadians” through accessible and easily understood health information, including product monographs. An increased focus on post-market surveillance through the MHPD, the report suggested, was part of the significant and on-going progress being made by Health Canada.

Paradoxically, it seemed that the department wanted, on the one hand, to avoid creating an impression that if it hadn’t been lax in its oversight of the health protection system that Vanessa Young might have avoided the drug that took her life, while on the other hand impressing upon a still critical and anxious public that it was responding positively to the tragedy. The report said Health Canada would make “health information even more readily available” than it did before; it would “enhance” product monographs by making them more intelligible to the general public; it would look for “better ways” to share information and, finally, it would increase the focus on post-market surveillance. But there appears to have been no critical “self-examination” to determine why the system of post market monitoring failed, or even a recognition that it did, in fact, fail. Although Health Canada had a critical opportunity to seriously analyse where the system had failed, its response to Vanessa Young’s death was essentially to provide the same services and more information about them.

On the important issue of information sharing, the report did not indicate when – or whether – it would implement the recommendations of the Coroner’s inquest that pharmaceutical companies be required to “clearly indicate information relating to adverse drug effects/contraindications on product monographs, promotional material and prescribing information”. Nor did the report indicate that Health Canada is moving towards a system of mandatory reporting by health professionals.

In spite of the obvious fact that Vanessa Young suffered from an illness linked to sex and gender, the August 2002 report did not pass through a “gender lens”. This would be necessary to develop an analysis of the issues that resulted in the failure of Health Canada to act sooner on the information about the risks associated with cisapride – and identify the remedies so it wouldn’t happen again. In 2000, Health Canada had unveiled its strategy to support a gender-based analysis in a document entitled “Health Canada’s Gender-based Analysis Policy”. It said the department would meet the goal of the GBA policy by “identifying gender equality issues and

²² “HPFB announces a new organisation: Marketed Health Products Directorate (MHPD)”, Letter to stakeholders from Diane Gorman, Assistant Deputy Minister, dated April 2, 2002

²³ See *Vanessa’s Story*, Scrip Magazine, June 2002

²⁴ *Response to the Recommendations to Health Canada of the Coroner’s Jury Investigation into the Death of Vanessa Young*, Prepared by The Health Products and Food Branch, Health Canada, August 27, 2002

proposing remedies to inequality in the areas of policy and program development or implementation, research, funding, data collection, surveillance, regulatory activities, health promotion, disease prevention, services to First Nations and Inuit, consultations or communication plans”.²⁵

Health Canada’s response to the Coroner’s investigation into Vanessa Young’s death failed to utilise the department’s own GBA policy. The response does not address the question of why Vanessa Young and so many other young women and girls suffer from eating disorders or suggest what strategies should be or are in place to respond to this illness. But more to the point, perhaps, it did not identify any strategies to educate young women about how to identify an adverse drug reaction, how to report them, or how to seek help if they felt they were suffering such an event. The report does not, in fact, contain a single reference to cisapride, bulimia, anorexia, women, girls, gender or sex. Thus an opportunity to apply Health Canada’s Gender-based Analysis was missed, as well as was the opportunity for important health education of girls and young women.

Does the system serve women?

During the 1990s Health Canada announced a number of programs and initiatives it said would ensure that its health and drug regulations and policies supported a women’s health strategy. These included:

- funding to the Canadian Women’s Health Network to support communications and information on women’s health;
- the Canadian Breast Cancer Initiative (incorporating the Canadian Breast Cancer Research Initiative);
- a four-point Women’s Health Strategy;
- the creation of five Centres of Excellence for Women’s Health;
- amendments to the Food and Drugs Act to require manufacturers to include women in clinical trials in the same proportion as are expected to use the drug being tested; and
- the implementation of a gender-based analysis across the department.

²⁵ Health Canada’s Gender-based Analysis Policy, p. 10. Published by authority of the Minister of Health, Public Works and Government Services Canada 2000.

Much of this activity is overseen by the Women's Health Bureau, created in 1993 and now functioning within the Health Policy and Communications Branch. The mandate of the Bureau was clarified in the federal government's "Plan for Gender Equality", published by Status of Women in 1995.²⁶ The document covered all government activities, but included a strong focus on health and health research affecting women. One of the eight objectives of the plan aimed to "Improve Women's Physical and Psychological Well-being" by advancing "a women's health strategy that fully acknowledges and responds to the nature of women's lives, in research, policy development and practices in the health sector". The document acknowledged that "Canada lacks a comprehensive source of data and analysis on women's health", a situation that compromised women's health status. It outlined an ambitious program of research through the Medical Research Council (transformed into the Canadian Institutes for Health Research) on health issues that specifically affected women, such as breast cancer, as well as on the impact of federal policies on women's health.

The Plan for Gender Equality recognised that "Responding appropriately to women's health needs requires a stronger information base and research capacity on women's health". It identified the need for policies to ensure women participated as subjects in clinical trials for new drugs, and committed the federal government to reviewing the issues of women's health research and to establishing new guidelines for federally funded research programs. However, nowhere in the plan was there mention of the dearth of information and data on how women responded to prescription drugs once they were approved and on the market.

In August 1999, Health Canada published its own plan of action, called Women's Health Surveillance, designed to assist the Laboratory Centre for Disease Control (LCDC) in developing a women's health surveillance system.²⁷ The task was divided into two parts:

1. identify the characteristics of an effective women's health surveillance system; and
2. ascertain the available data, and develop an appropriate analytic model to identify "which partners would be needed and what plan of action would permit LCDC to move in the recommended direction most rapidly and effectively".

The action plan's focus continues to be enhanced surveillance of the conditions that affect women and which may require drug therapy, but it does not address the issue of women's post-market experiences with prescription drugs.

It is perhaps too soon to evaluate whether the many recent changes to ADR reporting are having the desired effects. However, it is clear that the Women's Health Strategy has not been fully integrated in the reorganised health protection system. The creation of the Women's Health Bureau, policies that supported a Gender-Based Analysis, and the stated commitments to strengthen the post-market and health surveillance apparatus within Health Canada were all positive starts. However, these initiatives are floundering because of an apparent lack of political will within the department. The failure of Health Canada to utilise its own GBA policy in its response to the jury's recommendations during the Coroner's Inquest into the death of Vanessa Young is one example of a promising initiative falling by the wayside.

²⁶ *Setting the Stage for the Next Century: The Federal Plan for Gender Equality*, Status of Women Canada 1995

²⁷ Bégin, Monique et al., *Women's Health Surveillance; A Plan of Action for Health Canada*. Report of the Advisory Committee on Women's Health Surveillance, Government of Canada, Ottawa, 1999.

The reorganisation of the Health Protection Branch initiated in the late 1990s presented an opportunity to strengthen the system of post-market surveillance to ensure that the health of all Canadians was well-served – and that women’s health needs were more specifically addressed. The changes included the establishment of the Marketed Health Products Directorate in April 2002 to co-ordinate post-approval monitoring of marketed drugs. The Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) within the MHPD monitors adverse reactions to all drug products sold in Canada, including prescription, non-prescription, biological, complementary medicines and radio-pharmaceutical products. The program has an office in Ottawa, and five Regional Adverse Drug Reaction Reporting Centres across the country. (By contrast, in France, there are 30 regional reporting centres.) The CADRMP participates in the International Drug Monitoring Program run under the umbrella of the World Health Organisation to enable countries to share information and compare data on adverse drug reactions.

What is an Adverse Drug Reaction?

The World Health Organisation defines an adverse drug reaction as “an effect which is noxious and unintended, and which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.” Canada has adapted the WHO definition of adverse drug reaction in Canadian law as follows²⁸:

Adverse drug reaction means a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function; (*réaction indésirable à une drogue*)

Adverse event means any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction. (*incident thérapeutique*)

Serious adverse drug reaction means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalisation or prolongation of existing hospitalisation, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death; (*réaction indésirable grave à une drogue*)

Serious unexpected adverse drug reaction means a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug; (*réaction indésirable grave et imprévue à une drogue*)

The Canadian ADR Monitoring Program maintains a computerised database – called the Canadian Adverse Drug Reaction Information System (CADRIS) – with information about all reported adverse drug reactions. The CADRMP guidelines emphasise that the definition of an ADR “includes *any* undesirable effect suspected to be associated with drug use”, but does not require that a causal link be established before a report is submitted.²⁹ The program also accepts reports of “drug abuse, overdoses, drug interactions and unusual lack of therapeutic efficacy” that may be an unintended response to a prescription drug.

²⁸ Food and Drugs Act: Food and Drug Regulations (Schedule No. 844), November 7, 1995.

²⁹ Therapeutic Products Program: Guidelines for the voluntary reporting of adverse drug reactions by health care professionals, available at <http://www.hc-sc.gc.ca>.

There is some confusion over the terms “adverse drug reaction” and “adverse drug event” which are often used interchangeably. Barbara Noah, a research associate in Health Law & Policy, Center for Governmental Responsibility, University of Florida College of Law, has written that “an ‘adverse drug event’ (ADE) is a more inclusive term and refers to ‘an injury resulting from medical intervention related to a drug, including unpredictable side effects of drugs (such as a skin rash or anaphylaxis), foreseeable side effects such as nausea with chemotherapy, and unwanted effects resulting from errors’.”³⁰

The term “adverse drug event” is used interchangeably with “adverse drug reaction” in Health Canada’s post-market surveillance system, although the CADR Newsletter prefers the latter term. The Marketed Health Products Directorate is responsible for co-ordinating, monitoring and collecting “adverse reaction and medication incident data”. There is a lack of consistency within Health Canada, as well as in the medical community and health system generally about these terms.³¹

How Canada’s ADR System Works

In order to more fully understand whether the system serves the specific health needs of women, it is necessary to provide a brief overview of how ADRs are monitored in the post-market environment.

The design of the current ADR reporting system can be traced to 1990, when Dr Curt Appel, then Chief of the Adverse Drug Reaction Monitoring Division, Drugs Directorate at the HPB, implemented a new drug safety monitoring program. This move was part of a trend that was occurring internationally in which many countries were re-organising their drug safety programs. Canada's new drug safety monitoring program included new regulations for reporting adverse drug reactions by pharmaceutical companies, as well as regional centres. In 1991, Dr Appel and Lori J. Anderson of the Bureau of Pharmaceutical Surveillance launched the Canadian Adverse Drug Reaction Newsletter whose objectives included providing feedback on ADRs reported in Canada as well as drug safety information.³²

The establishment of Regional ADR Centres and the opening of a toll-free reporting number has helped ease the process of reporting and data collection. In 1996, 4,000 adverse drug reactions were reported to the HPB. In 1997, that number was 4,006, increasing to 4,663 in 1998, 5,688 in 1999, 7,361 in 2000 and 7,389 in 2001. The percentage of all reports received by regional ADR Centres has grown from 24.8% in 1997 to 32.1% in 2001, although the highest percentage – 44.1% – was recorded in 1999. But the most significant change has been in the number of reporters identified as “consumer/patient”, in spite of the absence of a formal process – including a communication strategy – to facilitate such consumer-reporting. In 1998, 7.1% of suspected

³⁰ Noah, Barbara, Adverse Drug Reactions in Elderly Patients: Alternative Approaches to Post-market Surveillance, *Journal of Health Law*, Summer, 2000, Vol. 33, No. 3, HOSPLW Pg. 383

³¹ A review of the CMAJ reveals a similar lack of consistency. For a representative example, see Letters, “Detecting adverse drug reactions”, David Rosenbloom and Christine Wynne, *CMAJ*, August 10, 1999,.

³² The CADRMP newsletter is readable, informative and also more accessible to consumers able to access the Internet. However, it should be more widely distributed, for example through hospitals, doctors offices, pharmacies and community health clinics. The newsletter also should highlight the ability of consumers to report adverse reactions directly on a toll free reporting line. In this the public can become better informed about the system itself, as well as the experiences others have had with prescription drugs and the regulatory role of Health Canada in drug safety.

ADRs were reported by patients/consumers, increasing to 9.1% in 1999, 13.7% in 2000, and 14.9% in 2001, the latest year for which statistics are available. Thus, the percentage of reports originating with consumers more than doubled in the three years between 1998 and 2001.³³

According to Heather Sutcliffe, the significant increase in the number of reports received in 1999 through Regional ADR Centres “may be related to increased awareness by physicians and pharmacists of these centres and the opening of the Ontario Regional ADR Centre in September 1998”.³⁴ The decline in the number of reports from Regional ADR Centres from 1999 to 2001, however, at the same time that reporting is on the rise, is a problem that should concern consumers, physicians and other health professionals. The Regional ADR Centres are contracted individually to large health institutions, typically hospitals. But they are grossly under-funded – the annual operating budget allocated to each Centre for staff, space, administrative services and program activities such as promotions is approximately \$35,000³⁵, with only one .5 FTE in each centre. Thus, while Regional ADR Centres can be linked to the significant increase in reporting from 1996 to 2001, the declines of the last two years may indicate that much more work – and money – is needed to sustain and expand access to the reporting system.

An effective communications strategy is an essential component in the ADR reporting system, and should include the collection of information that is then analysed and shared with the health care community and the public (while maintaining the confidentiality of the patient). An important objective of a communications strategy should be to ensure the information that is collected will influence therapeutic practice in a positive way.

Elements of such a strategy should include:

- a plan to encourage greater use of the ADR reporting system;
- a system to collate and analyse the information;
- a strategy to share ADR information with consumers and health professionals.

Mandatory versus voluntary reporting

Adverse drug reactions are reported voluntarily by doctors, pharmacists, allied health professionals and consumers. Manufacturers are required to report serious ADRs, but non-serious reactions are reported voluntarily. The largest percentage of reports are submitted by manufacturers, followed by Regional ADR Centres, hospitals, pharmacists, physicians and consumers. (It should be noted, however, that the reports filed by Regional Centres, the manufacturers and hospitals were, primarily, originally filed by health professionals (or, in some cases, consumers). Health professionals in hospitals, for example, will send their reports to the Pharmacy Dept which will then forward them; professionals in the community will either send reports to the manufacturer or the Regional Centres.)

³³ Adverse drug reaction reports are available in the Canadian Adverse Drug Reaction Newsletter, available on-line at <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/htmleng/cadrnewsletter.html>. The reports are also published regularly in the Canadian Medical Association Journal.

³⁴ Sutcliffe, Heather, Adverse drug reaction reporting, 1999 Canadian Medical Assn Journal, April 4, 2000.

³⁵ Functional Review of Post-Approval Drug Assessment Operational Activities For Therapeutic Products Programme, Bureau of Drug Surveillance, Prepared for the Continuing Assessment Division, Bureau of Drug Surveillance by the HDP Group Inc., Ottawa, 19 March 1999

Several important bodies have urged Health Canada to make reporting of adverse reactions by physicians and pharmacists mandatory, including the Krever Inquiry and the Coroner's Jury investigating the death of Vanessa Young. Even Canada's Auditor General, in a report in December 2000, said "Even if [Health Canada] could adequately process and disseminate post-market assessments, its ability to assess risks is limited given that health practitioners' reporting of post-market events is voluntary." The report went on to say "We recognise that Health Canada has no authority to compel physicians to report these events and that non-reporting is largely beyond its control because authority for medical practitioners rests with the provinces. However, the result of this weakness has been a long-standing concern for inadequate reporting."³⁶

Canada's system of drug regulation begins at the clinical trial stage, proceeds to the drug approval stage and concludes with promotion and post-market monitoring once the drug is on the market. Post-market surveillance in Canada is the weakest stage of drug regulation, with the lowest budget. In 1999, the Bureau of Drug Surveillance/Continuing Assessment Division had a complement of 37 full-time positions, and a budget of \$2.7million for prescription drug surveillance. At the time, this was the smallest allocation among all the bureaux in the Therapeutic Products Programme, with about 5.5% of the total TPP budget. The Bureau did not monitor all health products, but rather focused on pharmaceutical drugs, with responsibility for medical devices, biologics, vaccines, radiopharmaceuticals and veterinary drug products allocated among six other bureaux in the TPP.³⁷

The new directorate – MHPD – has a much broader mandate to monitor pharmaceuticals, biologicals, vaccines, medical devices, natural health products, radiopharmaceuticals and veterinary drug products. Its range of responsibilities has grown to include monitoring and collecting adverse reaction and medication incident data, reviewing and analysing marketed health product safety data, conducting risk/benefit assessments of marketed health products, communicating product related risks, overview of regulatory advertising activities, active surveillance and drug effectiveness project. Despite these expanded responsibilities, the MHPD was provided an initial allocation of only 35 scientific and 15 support staff. Its budget was set at \$10 million annually.³⁸

Under-funding of post-market surveillance undermines the effectiveness of the system, but so, too, does the lack of a strong political commitment to ensuring the system works well. Both of these aspects need to be strengthened. In addition, Canada's system of post-market surveillance should act on the recommendations of a growing number of groups and decide whether it will develop a mandatory system of reporting of adverse drug reactions by physicians and pharmacists. But it also must actively encourage consumers to report adverse reactions and implement a more formal and accessible process for them to do so.

³⁶ Report of the Auditor General of Canada - Chapter 26 Health Canada, Ottawa: December 2000

³⁷ Functional Review of Post-Approval Drug Assessment Operational Activities For Therapeutic Products Programme, Bureau of Drug Surveillance, Prepared for the Continuing Assessment Division, Bureau of Drug Surveillance by the HDP Group Inc., Ottawa, 19 March 1999

³⁸ *HPFB announces a new organisation: Marketed Health Products Directorate (MHPD)*, Health Canada: Ottawa, April 1, 2002

Prescription drug therapy is an increasingly important part of the treatment strategies employed by doctors, hospitals and other health professionals. An effective ADR reporting system should help develop and strengthen policies that enhance the ability to make such drug treatment safe and effective. Adverse drug reaction information, according to the CADRMP, is used to help ensure that the benefits of a drug continue to outweigh the risks, to ensure labels and product information remain current and up-to-date, and to inform Canadians about adverse drug reactions. But as , Dr Joel Lexchin - a Toronto physician who has extensively researched the drug industry - has said, Canada's regulatory system is "good at not letting drugs on the market. We're less good at getting them off if something goes wrong. And that's because Ottawa doesn't require post-marketing studies".³⁹

The inadequacies of a voluntary reporting system

Safe use of medicines depends on the availability and effective communication of reliable information, including adverse drug information. Canada's reliance on voluntary reports from physicians and pharmacists is known to pick up only a small proportion of adverse reactions. David Kessler, the former head of the US Food and Drug Administration, estimated that fewer than 1% of physicians ever made ADR reports on the drugs they prescribed.⁴⁰ A 1997 study of ADR reporting by family physicians in France found that an estimated one in 4500 serious drug reactions were reported in normal practice, based on the rate of reports in their monitoring study as compared to the normal number of reports over the same time period.⁴¹ A recent editorial in the Canadian Medical Association Journal pointed to "psychological and behavioural barriers to reporting [that] are not difficult to surmise," including the need for the physician to recognise that the reaction is caused by the drug, to judge that the event is worth reporting and to be willing to admit their own or a colleague's mistake.⁴²

In 1999, Duncan Hunter and Namrata Bains, in the Canadian Medical Association (CMA), estimated that an average of 16,344 hospital admissions each year in Ontario alone were for adverse drug reactions.⁴³ In a study published by the Journal of the American Medical Association, researchers estimated that in 1994 overall more than 2.2 million hospitalised patients in the United States had serious adverse drug reactions, while an additional 106,000 ADRs were fatal.⁴⁴ Based on a comparison of populations, the researchers estimated the number of deaths in Canadian hospitals would be roughly one-tenth the US figure, or 10,000 deaths each year.⁴⁵ One report published in the CMA Journal estimated approximately 1,825 deaths a year could be attributed to adverse drug experiences.⁴⁶

³⁹ Lynda Hurst, "Protecting our health: Is Ottawa doing its job?" March 25, 1989, Toronto Star

⁴⁰ Kessler DA. Introducing MedWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993; 269:2765-68.

⁴¹ Moride Y, Haramburu A, Requejo A, Bégau B. Under-reporting of adverse drug reactions in general practice. British Journal of Clinical Pharmacology 1997; 43(2):177-181

⁴² "Post-marketing drug surveillance: what it would take to make it work", CMAJ 2001; 165(10): 1293

⁴³ Hunter D, Bains N. Rates of adverse events among hospital admissions and day surgeries in Ontario from 1992 to 1997. CMAJ 1999; 160(1):1585-

⁴⁴ Jason Lazarou, MSc; Bruce H. Pomeranz, MD, PhD; Paul N. Corey, PhD, "Incidence of Adverse Drug Reactions in Hospitalized Patients, A Meta-analysis of Prospective Studies", Journal of the American Medical Association, Vol. 279 No. 15, April 15, 1998.

⁴⁵ Carolyn Abraham and Paul Taylor, "Drug reactions kill thousands: researchers", The Globe and Mail, April 15, 1998.

⁴⁶ Namrata Bains, MSc; Duncan Hunter, PhD, Adverse reporting on adverse reactions, CMAJ 1999;160:350-1.

According to David Rosenbloom and Christine Wynne, the annual number of deaths due to adverse drug reactions in Canada, using a 1:10 ratio of the population of Canada to that of the US, would total 7,600 annually – 10% of the estimated 76,000 deaths due to adverse drug reactions each year in the US.^{47 48} “This estimate would rank adverse drug reaction fatalities as the 7th leading cause of death in Canada, after cancer, heart disease, stroke, pulmonary disease and accidents, using 1995 Statistics Canada data,” they said, adding that “adverse drug reactions prolong hospital stay by an average of 4.6 days in Canada, costing Can\$300 million annually. In 1999 Lexchin offered an estimate of 2,925 deaths annually in Ontario alone due to adverse drug reactions.⁴⁹ On the other hand, Health Canada has attributed 1,417 deaths to ADRs between 1984 and 1994.⁵⁰

Lexchin has noted that the great variance in the estimates is partially due to complexities associated with recognising and reporting ADRs.⁵¹ These include: difficulty in discerning whether the death was caused by a pre-existing condition or a drug; multiple medications taken by many hospitalised patients; lack of practical definitions on the appropriate information to collect; and the lack of a standard approach to reporting ADRs.

Thus, the estimates regarding how many deaths due to adverse reactions are experienced each year in Canada vary widely, from a high of 10,000 to a low of 141 by Health Canada. It is now widely accepted that the number of adverse reactions reported to Health Canada represents a small percentage of the actual number experienced, pointing to the shortcomings of a voluntary reporting system. “In 1999,” reports Barbara Sibbald in the CMAJ, “more than 258,000 [adverse reactions] were reported in the US, so if Canadian reporting matched US levels, there would have been roughly 25 000 reports here.”⁵² The 7,389 reports filed in 2001 is nowhere near that number, suggesting that the number of reports filed in Canada may be in the range of 3% to 5%.

The issue of mandatory versus voluntary reporting is a complex one. Mandatory reporting by physicians and pharmacists seems like common sense but how this plays out in regular practice is less straightforward. Experience has shown that when health professionals feel they are being “policed”, their willingness to co-operate declines. Furthermore, there is no fool-proof way to police such a system; if it was determined that an ADR had not been reported, the health professional could claim they did not believe it was an ADR or that it was “common knowledge” and “not worth reporting”. Even in jurisdictions where mandatory reporting is required, sometimes it is simply ignored.⁵³

⁴⁷ Bates DW, Cullen DJ, Laird N, Peterson L, Small S, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. *JAMA* 1995;274:29-34.

⁴⁸ Rosenbloom, David, Wynne, Christine Detecting adverse drug reactions *CMAJ*, August 10, 1999; 161(3)

⁴⁹ Lexchin J. Rethinking the numbers on adverse drug reactions [letter]. *CMAJ* 1999;160:1432.

⁵⁰ Mittman, Liu BA, Iskedjian M, Bradley CA, Pless R, Shear NH, et al. Drug-related mortality in Canada (1984-1994). *Pharmacoepidemiology Drug Safety* 1997;6:157-68.

⁵¹ Lexchin, J. Adverse Drug Reactions: Review of the Canadian Literature. *Canadian Family Physician*, Vol 37, January 1991; 109-118.

⁵² Sibbald, Barbara, Cisapride, before and after: still waiting for ADE-reporting reform *CMAJ*, November 13, 2001; 165 (10)

⁵³ Rick Weiss & Deborah Nelson, “Victim's dad faults gene therapy team”, *Washington Post*, Feb. 3, 2000, A2.

However, when there is sufficient education and publicity about not just the requirement of reporting but the importance of doing so, reporting increases. The case of silicone gel breast implants in the United States demonstrates that when awareness on the part of health professionals and the public is heightened, reporting increases significantly.⁵⁴

If any system of mandatory reporting were to be instituted, it would be *critical* for it to be supported by additional educational resources (both during training and continuing medical education) as well as initiatives to better publicise the need for such reporting. At the very least, disincentives to reporting should be removed by making the process quick and efficient, and ensuring that physicians and pharmacists who report also receive information back.

ADR Reporting: Gender differences

The inadequacies in the drug safety and post-market surveillance systems affect all communities, but those already confronting inequities based on gender, race and ethnicity may be exposed to greater risk. The absence of a strategy to systematically collect, investigate, analyse and interpret data on adverse reactions and other side effects may undermine efforts to develop an effective public health policy affecting women.⁵⁵

There is mounting evidence that gender is a significant risk factor for adverse drug reactions, which occur in women at a higher rate in both hospital and community settings. Female patients are estimated to have a 1.5- to 1.7-fold greater risk of developing an adverse reaction to drugs, including adverse skin reactions, compared with male patients.⁵⁶ The reasons are not wholly understood, however the differences cannot be attributed solely to patterns of use.

In January 2001, the US General Accounting Office informed the Senate and the House of Representatives that, “eight of the 10 prescription drugs withdrawn since January 1, 1997, posed greater health risks for women than for men”. For four of the withdrawn drugs, the report said, “the greater health risk may have been due to a higher level of use among women”. But four other withdrawn drugs posed greater health risks for women even though they were widely prescribed to both women and men. “Greater health risks for women may be due to physiological differences that make women differentially more susceptible to some drug-related health risks,” concluded the report.⁵⁷

⁵⁴ 1998 U.S. Department of Health and Human Services; Public Health Reports; 113: 535-543, November/December, 1998. Commentary on Immunization Registries Silicone Gel Breast Implant Adverse Event Reports to the Food and Drug Administration, 1984-1995, S. Lori Brown, PHD MPH; Christine M. Parmentier, RN MPH; Eileen K. Woo, RN; R. Lakshmi Vishnuvajjala, PHD; Marcia L. Headrick, DVM MPH

⁵⁵ Other risk factors include class, ethnicity, race, disability and age. However, for the purposes of this study I have identified only gender, which crosses all these categories.

⁵⁶ Rademaker, M., Do women have more adverse drug reactions? [In Process] Am J Clin Dermatol 2001; 2 (6): 349-51

⁵⁷ Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women”, United States General Accounting Office Washington, DC, GAO 01-286R. The GAO did not look at over-the-counter drugs or vaccines.

According to Catherine White, an Associate Professor in the Department of Pharmaceutical and Biomedical Sciences, University of Georgia, “The increased incidence of adverse drug reactions [among women] may result from many influences including gender-related differences in pharmacokinetics/pharmacodynamics, hormonal changes, use of medications which inhibit drug metabolism (exogenous hormones), higher prevalence of drug usage in women, and differences in reporting rates.”⁵⁸ She added that since “sex/gender clearly influences the pharmacokinetics of some drugs, it should also be expected to play a significant role in the incidence and severity of drug interactions”.

Thus, among certain groups – for example, those with HIV/AIDS – women may be at increased risk because they are using multiple drug therapy, one known risk factor, and because they are female, another possible risk factor. Although it is not known if sex/gender-based drug interactions are responsible for the increased adverse reactions associated with drug therapy in women, it is very clear that much more research is needed to determine the effects it may have on this area.

This type of research cannot be undertaken in Canada until a system is in place to collect, organise and maintain data that identifies the sex of the patient. At the very first step in the reporting process, regardless of who is reporting, there are barriers to developing a gender-based analysis of the experience Canadians have with prescription medicines. According to Lynn MacDonald of the Marketed Health Products Directorate, the information in filed ADR reports is required to identify:

- a) that a patient existed;
- b) the suspect product;
- c) the suspect reaction and
- d) the reporter.⁵⁹

While the identification of sex in ADR reports may be – and usually is – submitted voluntarily, it is not required. The only Canadian study of gender-related differences in adverse drug reactions found by this writer examined patient data from the Sunnybrook Health Science Centre ADR Clinic covering the period from April 1986 to May 1996. The study found that female gender is a risk factor for the development of adverse drug reactions, but concluded that “Further work is required to elucidate the mechanisms explaining the differences observed between male and female patients”. In order for such work to be conducted in Canada, there must be a more systematic and purposeful collection of data.⁶⁰

⁵⁸ Catherine White, Ph.D., Gender Effects on Pharmacotherapy, Department of Pharmaceutical and Biomedical Sciences, University of Georgia, paper presented to the Conference on Biologic and Molecular Mechanisms for Sex Differences in Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics, May 5, 1999. The conference was sponsored by the U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Agenda for Research on Women’s Health for the 21st Century. A Report of the Task Force on the NIH Women’s Health Research Agenda for the 21st Century, Volume 2. Bethesda, MD. NIH Publication No. 99-4386. 1999.

⁵⁹ Telephone interview, May 6, 2002.

⁶⁰ Tran C, Knowles SR, Liu BA, Shear NH, Gender differences in adverse drug reactions. *J Clin Pharmacol* 1998 Nov; 38(11):1003-9

Yet, according to Susanne Reid, Manager – HIV Therapies Enhanced Surveillance Project, Active Surveillance Division, MHPD, “No specific guidelines for the evaluation of gender, gender-related differences, and other sub-population differences have been developed to date” within the health protection system. Similarly, “the Therapeutic Products Directorate’s pre-market pharmaceutical review bureaus do not look systematically at the ADR reports from a gender point of view.” Ms Reid said the MHPD anticipates the directorate will develop guidelines to evaluate gender-related differences in adverse reactions to prescription drugs “sometime in the future”. Currently, however, the post-market drug surveillance system is unable to support a women’s health strategy.⁶¹ The negative consequences of inadequate resources for Canada's ADR reporting system are demonstrated once again.

There also is a need to understand more about the consumers who report adverse drug reactions. Logic would suggest that a majority of consumers who do access the Regional ADR Centres or the toll free telephone line are women reporting on their own behalves, or on behalf of a partner or children. But sex is not identified, and so we have no information about what strategies might be effective in encouraging consumers to report. If we had adequate information about who is reporting, education and publicity could be tailored to those groups most likely to report (i.e if women, publicity could be enhanced in women's magazines and through other avenues more frequented by women).

The lack of a strategy to collect and evaluate data on women and adverse drug reactions raises concerns for a number of reasons, including that such serious information gaps undermine our ability to develop evidence-based strategies designed to meet the needs of Canadian women. A solid information base would also permit Canada to contribute to international efforts to identify gender-related trends in prescription drug experience (such as the International Drug Monitoring program of the WHO).

But most importantly, Canadian women have a right to be warned about drugs that may harm them, and that includes access to the experiences other women have already had before them. Health Canada has both a mandate and a responsibility to ensure this happens, and that the commitments to a strong women’s health strategy that includes post-market surveillance are acted upon.

Conclusion

The current system of post-market surveillance does not serve Canadians well, regardless of their sex. Despite a number of strong and positive initiatives within Health Canada to support strategies that support women’s health, the regulations in place to ensure women are protected once drugs are on the market are very weak. The programs and policies – including the Women’s Health Bureau, the Gender-Based Analysis and the federal government’s “Plan for Gender Equality” – might have a positive influence on the system of post-market surveillance if that system is adequately funded. In addition, there must be a stronger political will to ensure that

⁶¹ Susanne Reid, HIV Therapies Enhanced, Surveillance Project, Active Surveillance Division Personal correspondence with the author, dated 06 August 2002.

Canada's prescription drug surveillance is transparent, that information about drug safety and ADR experiences flows both to and from consumers. None of these elements are currently in place.

Recommendations from Women and Health Protection

Preamble

To be truly responsive to public health needs, Canada's drug approval system needs to be strengthened. New drugs should only be allowed if they show an advantage over existing treatments, whether it is an advantage of safety, effectiveness or convenience. Currently decisions are made behind closed doors with no public input into the process or access to the information on which decisions are based. We need a drug approval system which allows a participatory process and full public access to the information on drug safety and effectiveness used by Health Canada in its assessment. This should include specific attention to gender and consultation with women's organizations if a drug or device is being considered for use either only or mainly by women. It should also include clear conflict-of-interest guidelines for scientific, advisory and decision-making committees involved in drug regulation.

We recommend that the Office of the Auditor General of Canada:

undertakes a full inquiry into the process surrounding the post-marketing surveillance of prescription drugs to determine: i) the extent to which changes have occurred since the Auditor General's investigation of 1987 and ii) the extent to which the recommendations made to Health Canada in the verdict of the Coroner's Jury (Vanessa Young Inquiry) have been followed up on.

We recommend that the Marketed Health Products Directorate:

1. develops a comprehensive strategy for post-market safety of women's experiences with prescription drugs. Such a strategy should be developed in consultation with the women's health community and include the principle of the right to be warned and informed.
2. expands regional reporting centres and adequately funds these as the front lines of the reporting system, in addition to continuing to promote reporting nationally through the Adverse Reaction Information Unit.
3. removes the barriers to reporting which exist and strengthens the mechanisms for reporting by consumer and patient advocacy groups which are currently in place, in addition to enhancing reporting mechanisms for physicians, pharmacists and manufacturers. This should include such measures as: raising awareness of the importance of reporting in training programmes and continuing medical education; actively promoting the importance of consumer reporting of ADRs through a public awareness campaign; and insuring that all dispensed medicines are accompanied by written approved product information (the Patient

Product Monograph) which include information on how to report ADRs. One method of encouraging physicians to report ADRs would be that they receive continuing medical education credits for doing so.

4. allows open public access, through a computerised database posted on the web, to aggregated information on adverse drug reactions reported in Canada and internationally for all drugs marketed in Canada. This should include breakdowns by age groups and by sex. If a serious drug safety concern arises, the Directorate should send out "Dear Health Professional" letters directly, rather than relying on the manufacturers. Media and consumer advisories should accompany such letters to inform the public of such warnings. Health professional letters and media and consumer advisories must include age and sex analyses as well as types of reported serious adverse events and deaths, if they have occurred. Warnings should be disseminated to health professionals and the public not only if a problem is suspected in Canada, but also if a drug has been banned or restricted for safety reasons in another country. The financing of production and dissemination of such letters and media advisories should be the responsibility of the manufacturer but the content should be entirely the Directorate's responsibility. The Directorate should test different strategies for disseminating these warnings effectively and expeditiously to the public and health professionals.
5. makes systematic, scientifically designed post-market follow-up studies during the first years of a drug's use a condition of licensing for drug manufacturers. The results of such studies should be reported in a manner which includes attention to sex differences. These post-approval studies should not be a trade-off for weaker drug approvals.
6. monitors the reporting of drug manufacturers to ensure they are fulfilling their obligations under existing regulations, and ensures that manufacturers conform to the objectives of Health Canada's Women's Health Strategy.